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NEPHROLOGY FORUM

Hyperkalemic hyperchloremic metabolic acidosis: Pathophysiologic insights

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Case presentation

A 28-year-old woman with acquired immunodeficiency syndrome manifest as HIV (CD_4 T-cells $<10/mm^3$) and opportunistic infections (prior cerebral toxoplasmosis and *Pneumocystis carinii* pneumonia) was admitted to Hermann Hospital-University of Texas, Houston, with severe dyspnea and chest pain. An initial chest radiograph revealed bilateral pleural effusions and massive cardiomegaly. Echocardiography demonstrated a large pericardial effusion, and a pericardiotomy with window was performed on the first hospital day. Although the patient improved subjectively, she remained febrile, and on the second hospital day pentamidine was administered on the assumption that the *Pneumocystis carinii* pneumonia had recurred.

Laboratory values on admission were: BUN, 27 mg/dl; creatinine, 1.2 mg/dl; sodium, 138 mEq/liter; potassium, 4.1 mEq/liter; chloride, 107 mEq/liter; and bicarbonate, 23 mEq/liter. Three days after initiation of pentamidine, the chemistries were as follows: BUN, 72 mg/dl; serum creatinine, 2.7 mg/dl; sodium, 139 mEq/liter; potassium, 6.8 mEq/liter; chloride, 111 mEq/liter; bicarbonate, 13 mEq/liter, and serum osmolality, 307 mOsm/kg H_2O; the Nephrology Service was consulted. The following urinary chemistries were obtained at that time: sodium, 40 mEq/liter; potassium, 49 mEq/liter; chloride, 32 mEq/liter; creatinine, 79 mg/dl; and osmolality, 419 mOsm/kg H_2O. The calculated transtubular potassium gradient (TTKG) was 6.0, and the urine net charge (UNC) was +57 mEq/liter. Despite severe hyperkalemia and metabolic acidosis, the electrocardiogram revealed a normal sinus rhythm. Kayexalate was given rectally and the potassium declined to 5.9 mEq/liter in 12 hours. Pentamidine administration was discontinued and bicarbonate was administered intravenously. The serum potassium declined to 3.5 mEq/liter within 24 hours.

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Discussion

DR. THOMAS D. DUBOSE, JR. (*Director, Division of Renal Diseases and Hypertension, and Professor of Internal Medicine and Integrative Biology, University of Texas Medical School, Houston, Texas, USA*): This case represents a problem encountered commonly by internists and nephrologists: hyperchloremic metabolic acidosis with hyperkalemia and renal insufficiency in association with drug nephrotoxicity. Hyperkalemic hyperchloremic metabolic acidosis invariably indicates an abnormality in potassium, ammonium, and hydrogen ion secretion which, while most evident in patients with renal insufficiency, is not always the result of a reduction in renal mass. Indeed, the decrease in whole-kidney potassium and ammonium excretion is usually out of proportion to the degree of renal insufficiency (as defined by a decrease in glomerular filtration rate) and often can be attributed to a generalized defect in renal tubular function in the cortical and/or medullary collecting ducts. In this discussion, I will review the physiology and pathophysiology of potassium and ammonium excretion, and I will focus on the interrelationship between potassium and ammonium transport as it pertains to the pathophysiology of the clinical syndrome of hyperkalemic hyperchloremic metabolic acidosis.

Renal potassium secretion

The renal contribution to potassium balance is a homeostatically regulated process accomplished through regulation of potassium secretion across the apical membrane of principal cells in the cortical collecting duct. The quantity of potassium secretion depends on the apical membrane potassium conductance and the electrochemical driving force across the apical membrane. Potassium conductance is defined as the sum of the collective potassium channels in the apical membrane. Variables that regulate potassium secretion in this nephron segment include factors that affect the potassium conductance (for example, urine flow and sodium delivery) and factors that regulate the electrochemical driving force (for example, potassium balance, transepithelial potential difference, the pH and bicarbonate concentration of tubule fluid, systemic acid-base balance, and aldosterone) [1]. The electrochemical driving force for potassium secretion is maintained by the basolateral Na^+-K^+-ATPase (that is, the "sodium pump"). Sodium absorption through apical sodium-selective channels maintains the negative potential difference in the tubular lumen. The sodium pump generates a negative lumen potential and a high intracellular potassium concentration, which together augment potassium secretion. An early effect of aldosterone is

increased activity of the apical sodium-selective channel; with time, aldosterone also increases the activity of the basolateral Na^+-K^+-ATPase. As expected for a homeostatically regulated process, potassium secretion varies in parallel with systemic potassium balance (that is, potassium secretion increases dramatically in acute and chronic hyperkalemia, and decreases in hypokalemia) [1].

Renal potassium excretion is primarily the result of regulation of tubular potassium secretion. It therefore follows that a clinical estimate of potassium transfer into the cortical collecting duct could be helpful in the recognition of hyperkalemia of renal origin. The transtubular potassium gradient (TTKG) [2] has emerged as a clinically useful tool for estimating the potassium concentration "gradient" between the peritubular capillary and the tubular lumen at the level of the cortical collecting duct (CCD). A low TTKG in the hyperkalemic patient (<8) implies that the collecting tubule is not responding appropriately to the prevailing hyperkalemia and that potassium secretion is impaired. The formula defining the TTKG follows:

$$\text{TTKG} = \frac{[K^+]_u / [K^+]_p}{U_{Osm}/P_{Osm}}$$

where $[K^+]_u$ and $[K^+]_p$ represent potassium concentration in the urine and plasma, respectively, and U_{Osm} and P_{Osm} represent urine and plasma osmolality respectively. In this expression, the urine-to-plasma potassium concentration ratio is corrected for water abstraction in the more distal segments of the collecting duct. The TTKG computation assumes no significant alteration in potassium content between the CCD and final urine; that CCD tubular fluid osmolality is approximately the same as plasma osmolality; that "osmoles" are not extracted between CCD and final urine; and that plasma $[K^+]$ approximates peritubular fluid $[K^+]$ [3]. Under certain clinical conditions, some or none of these assumptions might be entirely correct [1]. Particularly problematic is the effect on the TTKG of a dilute urine or of high urine flow rates (polyuria). In these situations, the TTKG underestimates potassium secretory capacity in the hyperkalemic patient. With consideration for these potential pitfalls, the TTKG appears to be a useful clinical tool for estimating potassium secretory ability, but it might be no more useful than is the fractional excretion of potassium (FE_{K^+}). Because the hyperkalemia of mineralocorticoid deficiency should respond to mineralocorticoid replacement, a patient with hypoaldosteronism would be expected to exhibit an increase in the TTKG after fludrocortisone administration for several hours; the TTKG would not be expected to be altered in a patient with resistance to mineralocorticoid. Thus, an increase in the TTKG to >8 after mineralocorticoid administration suggests aldosterone deficiency; failure of the TTKG to increase suggests tubular insensitivity to mineralocorticoid (pseudohypoaldosteronism, voltage defect) [4]. The renal causes of hyperkalemia, which may be evidenced by an inappropriately low TTKG in the presence of hyperkalemia, are reviewed in Table 1.

Table 1. Causes of hyperkalemia attributed to decreased potassium excretion

Decrease in distal flow rate
Decrease in sodium delivery
Decrease in secretion of renin or aldosterone
Renal secretory defects
Primary
Secondary
Drugs/toxins
Interstitial diseases

Renal ammonium production and transport

Several nephron segments possess ammoniagenic enzymes, but the majority of ammonium excreted in the urine is derived from the metabolism of glutamine in proximal tubule cells [5–7]. Ammonium production in the proximal tubule is regulated through the pivotal enzymes glutaminase and phosphoenolpyruvate carboxykinase. In chronic acidosis, the activities of both enzymes and the abundance of their respective messenger RNAs increase [8, 9]. At physiologic pH, two ammonium ions and the divalent anion alpha ketoglutarate (ultimately metabolized to two bicarbonate ions) are the major products of glutamine metabolism. Figure 1 depicts the nephron segments responsible for ammonium transport and its regulation. Ammonium is preferentially secreted into the proximal tubular lumen across the apical membrane [10–13]. Most of the ammonium is secreted in the first portion of the proximal convoluted tubule [10]. Direct ammonium secretion occurs via substitution of ammonium for hydrogen ion on the apical membrane Na^+/H^+ exchanger [10, 11]. In the S_3 segment of the proximal straight tubule, ammonium secretion is increased by the presence of an acid disequilibrium pH [14].

As fluid leaves the proximal tubule and enters the loop of Henle, a number of processes lead to ammonium and ammonia efflux and result in a high medullary interstitial ammonium concentration. When fluid delivered out of the proximal tubule is alkalinized in the thin descending limb by water abstraction [15], a milieu favorable for ammonia efflux by non-ionic diffusion is created (Fig. 1). Direct ammonium transport across the medullary thick ascending limb of Henle's loop (mTALH) apical membrane (by substitution of ammonium for potassium on the Na^+-$2Cl^-$-K^+ cotransporter) is the major mechanism for absorption and is responsible for generation of high medullary ammonium concentrations [16]. Evidence for this mechanism is the observation that ammonium absorption is attenuated by luminal application of furosemide and is competitively inhibited by increasing concentrations of potassium [17]. In addition, ammonium also might be absorbed across the apical membrane of the mTALH through barium-sensitive and -insensitive potassium channels. However, the physiologic significance of the Na^+-$2Cl^-$-K^+ cotransporter for ammonium absorption is better understood [18]. The pathway for ammonium exit across the basolateral membrane is not clearly defined but likely is achieved through substitution for potassium on the basolateral potassium conductance [17]. A highly selective potassium channel that is sensitive to ATP (ROMK-II) has been cloned and localized to the mTALH [19] and could represent a channel that is responsible for ammonium uptake across either membrane of the mTALH.

Ammonia can re-enter the proximal straight tubule from the interstitium [14], thus leading to countercurrent multiplication, where the "single effect" involves selective addition of ammonium by the proximal tubule and active ammonium absorption in the thick ascending limb of Henle's loop. The countercurrent system in the loop then multiplies the effect. The net result of this system is an axial gradient for ammonium. Thus, medullary concentrations of ammonium exceed cortical concentrations severalfold [20]. As a consequence, the concentrations of ammonium and ammonia in the medullary interstitium exceed the concentration

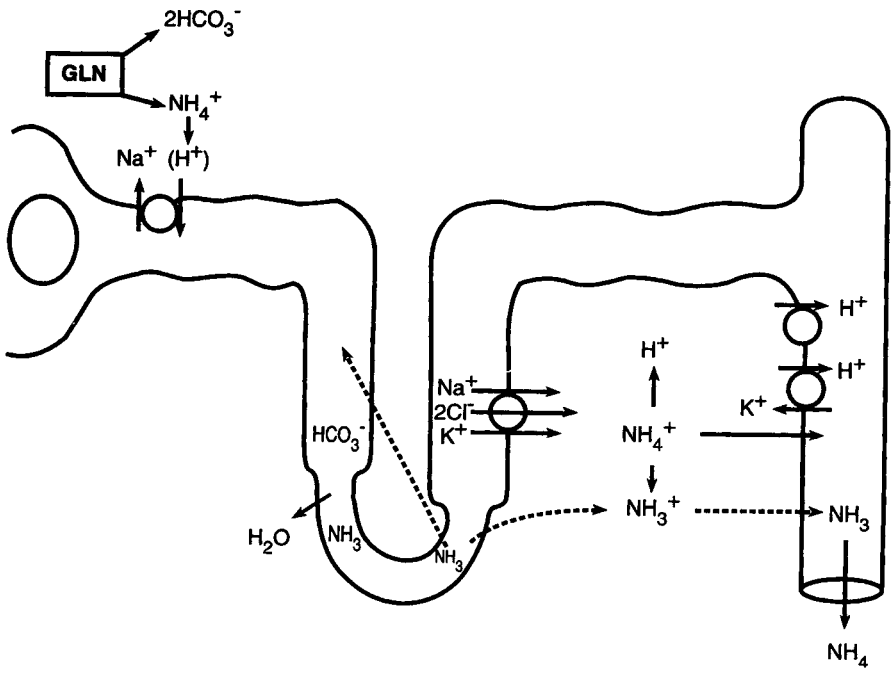

Fig. 1. *Nephron segments responsible for ammonium excretion.* Ammonium excretion is regulated in response to changes in systemic acid-base and potassium balance. Segmental contributions include: proximal convoluted tubule, proximal straight tubule, thin descending limb, thick ascending limb, and medullary collecting duct. GLN = glutamine.

prevailing in the inner medullary collecting duct (IMCD) lumen. Thus, a concentration gradient favorable for entry into the medullary collecting duct is created. Ammonium concentrations in the inner medullary interstitium reach the greatest amplification over cortical levels during chronic metabolic acidosis [21]. The high concentration of ammonium in the inner medulla can be obliterated by medullary washout and selective medullary destruction (for example, in chronic tubulointerstitial diseases).

Ammonium is secreted from the medullary interstitium into the medullary collecting ducts by a combination of ammonia diffusion and active hydrogen ion secretion (H^+-ATPase and H^+-K^+-ATPase). These processes result in high concentrations of ammonium in final urine. In addition, ammonium entry into the terminal IMCD (tIMCD) cell on the basolateral membrane is also accomplished by competition of ammonium for potassium on the sodium pump (Na^+-K^+-ATPase) [22]. A role for the Na^+-K^+-ATPase in ammonium transport in other collecting duct segments has not been established, however. The final step in ammonium secretion into the lumen of the tIMCD has not been elucidated unambiguously. It is generally assumed that ammonia diffuses across the apical membrane of the tIMCD in parallel with hydrogen ion secretion. An additional possibility, as displayed in Figure 2, is through an ROMK channel in the apical membrane in competition with potassium. Pathways for ammonia/ammonium transport in the medulla are summarized in Figure 2.

Metabolic acidosis increases ammonium production through stimulation of glutaminase and phosphoenolpyruvate carboxykinase primarily in the proximal tubule [7, 8, 23]. Moreover, in chronic metabolic acidosis, net ammonium addition to the proximal tubule is increased through augmentation of early proximal tubule ammonium secretion [7]. Therefore, ammonium delivery out of the late proximal tubule is increased dramatically. In response to the increase in delivery, ammonium absorption by the thick ascending limb of Henle's loop is augmented, thus increasing inner medullary interstitial concentrations of ammonia [23]. As a consequence of inner medullary accumulation of ammonia and the increase in the acid disequilibrium pH in the inner medullary collecting duct, ammonium addition to the medullary collecting duct increases [21].

The kidney's response to chronic metabolic acidosis is an increase in ammonium production and excretion. Therefore, in a patient with chronic metabolic acidosis of non-renal origin (whether of high or normal anion gap varieties), an increase in ammonium excretion ensues. Renal tubular disorders, such as the renal tubular acidoses (proximal, classical distal, and the generalized distal defect with hyperkalemia), are associated with an inappropriately low ammonium excretion rate when the degree of systemic acidosis is taken into consideration. In the absence of a laboratory determination of ammonium concentration in the urine, the urine anion gap (or the urine net charge) has been widely accepted as an indirect, clinical means of estimating the response of urinary ammonium excretion to metabolic acidosis. This calculation is based on the relative constancy of the unmeasured cations, such as magnesium and calcium (excluding ammonium), and unmeasured anions such as phosphate, sulfate, and organic anions present in the urine. In a person ingesting an average North American diet, the unmeasured anions exceed the unmeasured cations by approximately 80 mEq/day; thus on a daily basis, the sum of urinary $Na^+ + K^+ + NH_4 = Cl^- + 80$ [24]. Urinary ammonium concentrations usually are estimated from a spot urine by calculating the urine net charge (UNC) thus:

$$UNC = [Na^+ + K^+]_u - [Cl^-]_u$$

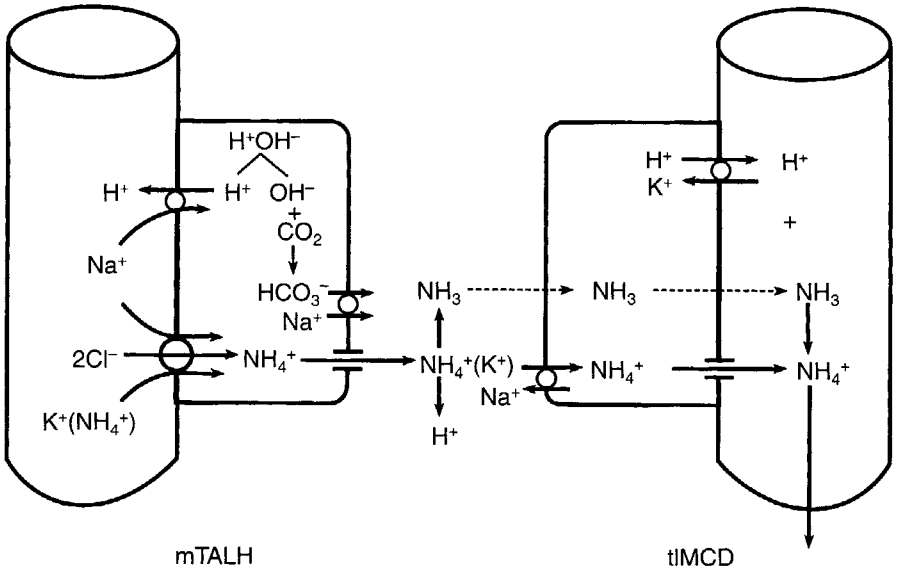

Fig. 2. *Relationship between ammonium transport in the medullary thick ascending limb of Henle's loop (mTALH) and the terminal inner medullary collecting duct (tIMCD).*

where u indicates urinary concentration. Hyperchloremic metabolic acidosis due to gastrointestinal losses can be differentiated in the laboratory from a renal defect in ammonium excretion, as urinary ammonium excretion is typically low in renal tubular abnormalities and high in patients with extrarenal bicarbonate loss (for example, diarrhea). As illustrated by the case presentation, the urine net charge of +57 predicts that little, if any, ammonium is present in the urine, signifying that the metabolic acidosis is of renal origin. The calculation of the urine net charge from a spot urine is derived from consideration of total daily excretion of unmeasured anions and cations. Thus it is more accurate when the daily urine volume is approximately one liter. The higher the urine output, the more unreliable the urine net charge will be in predicting the urinary $[NH_4^+]$. In polyuric states, the calculation of the urinary osmolal gap may be more precise [24, 25]. The utility of the urine net charge in estimating urinary ammonium excretion in metabolic acidosis is also affected adversely by ketonuria or the presence of drug anions in the urine. Calculation of $[NH_4^+]$ in the urine using the urinary osmolal gap should not be affected adversely by ketoacids, hippurate, or drug anions in the urine. Since this estimation has not been validated in a wide variety of clinical circumstances and has a number of potential pitfalls, the most reliable method for detecting a low ammonium excretion ratio is by direct measurement of urinary $[NH_4^+]$ in the clinical laboratory. If the urine sample is diluted 1:100, and if appropriate standards are run, the determination of the urinary $[NH_4^+]$ will be accurate.

Relationship between potassium and ammonium production and transport

Hyperkalemia should be regarded as an important determinant of the renal response to changes in acid-base balance. Potassium status can affect distal nephron acidification both by direct and indirect mechanisms. First, the level of potassium in systemic blood is an important determinant of aldosterone secretion, which in turn is an important determinant of distal hydrogen ion secretion. Further, studies in our laboratory over the last five or so years have established a critical role for potassium in ammonium synthesis in the proximal tubule and in ammonium excretion [26–28]. Chronic potassium deficiency increased, while chronic hyperkalemia suppressed, ammonium production [26]. These changes in ammonium production also affect medullary interstitial ammonium concentration and buffer availability [27]. Moreover, the effects of potassium balance on ammonium transport in proximal tubule and the thick ascending limb of Henle's loop have been demonstrated [29]. Hyperkalemia had no effect on ammonium transport in the superficial proximal tubule but markedly impaired ammonium absorption in the thick ascending limb, reducing inner medullary concentrations of total ammonia and decreasing secretion of ammonia into the IMCD [26, 29]. The mechanism for impaired absorption of ammonium in the TALH is competition between potassium and ammonium for the potassium secretory site on the Na-2Cl-K transporter, and perhaps for the apical (and basolateral) potassium channel as well [17, 18]. Hyperkalemia also might decrease entry of ammonium into the medullary collecting duct through competition of ammonium and potassium for the potassium-secretory site on the basolateral membrane sodium pump [18].

In summary, hyperkalemia can dramatically affect ammonium production and excretion. Chronic hyperkalemia decreases ammonium production in the proximal tubule and whole kidney, inhibits absorption of ammonium in the mTALH, reduces medullary interstitial concentrations of ammonium and ammonia, and decreases entry of ammonium and ammonia into the medullary collecting duct. The potential for development of a hyperchloremic metabolic acidosis is greatly augmented when renal insufficiency coexists with the hyperkalemia, or in the presence of aldosterone deficiency or resistance. Such a cascade of events helps to explain, in part, the hyperchloremic metabolic acidosis and reduction in net acid excretion characteristic of several experimental models of hyperkalemic-hyperchloremic metabolic acidosis, including obstructive nephropathy, selective aldosterone

Table 2. Animal models of hyperkalemic hyperchloremic metabolic acidosis

Chronic amiloride administration: voltage defect
Post-obstructed kidney: pump defect
Selective aldosterone deficiency: Pump/voltage/NH_4^+ deficiency
Chronic dietary hyperkalemia: NH_3/NH_4^+ deficiency

deficiency, chronic amiloride administration, and chronic dietary hyperkalemia in the rat [26, 30, 31].

Acidification defects associated with distal nephron dysfunction

Experimental models. Experimental models of hyperkalemic hyperchloremic metabolic acidosis have done much to elucidate the mechanisms responsible for this acid-base alteration (Table 2).

Chronic amiloride administration. Studies in our laboratory that employed microelectrodes to measure disequilibrium pH as an index of proton secretion, as well as PCO_2 in the papillary collecting duct in rats after administration of amiloride for four days, revealed that this model of hyperkalemia and metabolic acidosis is associated with a reduction in proton secretion. Impaired potassium secretion in the CCT, the result of such a "voltage" defect, resulted in hyperkalemia [32, 33].

Unilateral ureteral obstruction (UUO). Another experimental model of distal renal tubular acidosis associated with hyperkalemia is that secondary to unilateral ureteral obstruction. While findings in the postobstructed kidney are similar in many respects to the amiloride model discussed previously [30, 33], several lines of evidence clearly indicate that this disorder results from a non-voltage-mediated rate defect rather than a "voltage" defect. In the postobstructed model, the animal is unable to acidify the urine after an acid challenge, ammonium excretion decreases, the acid disequilibrium pH is obliterated, and the papillary PCO_2 is markedly reduced [30]; all these sequelae are compatible with a hydrogen ion pump defect. The decrease in ammonium entry into the inner medullary collecting duct appears to be the consequence, in part, of the defect in hydrogen ion secretion. The decrease in bicarbonate transport ($JtCO_2$) observed in vitro in perfused collecting ducts from rabbits subjected to ureteral obstruction appears first in medullary segments [34]. After UUO, H^+-ATPase activity is reduced to a greater extent in medullary than in cortical segments [35]. With immunocytochemical techniques, interruption in the cellular distribution of the 31 kD subunit of H^+-ATPase has been reported in rat intercalated cells [36]. This alteration suggests that the H^+-ATPase fails to insert into the apical membrane ("gaps" or "discontinuity") [36]. In summary, biochemical, in-vitro microperfusion, and in-vivo micropuncture studies support the view that the proton pump is impaired in unilateral ureteral obstruction.

Selective aldosterone deficiency. Selective aldosterone deficiency in the rat impairs hydrogen secretion by the inner medullary collecting duct [31]. This study also demonstrated impaired ammonium transfer from the interstitium into the IMCD lumen. As a result, ammonium excretion was reduced dramatically. Moreover, as a result of impaired ammonium production, ammonium delivery to the loop of Henle also was reduced. Thus, the reduction in ammonium transfer to the IMCD could be explained by a decrease in inner medullary ammonium accumulation. Since papillary PCO_2 was reduced during bicarbonate loading, the rate of proton secretion also was clearly compromised. Findings in experimental animals and in patients with adrenal insufficiency [37–39] provide evidence that mineralocorticoid deficiency can cause acidosis and impairment of renal acidification, even in the absence of renal disease or glucocorticoid deficiency. The potential for systemic metabolic acidosis in such a setting can be amplified greatly, however, in individuals with renal insufficiency and a decrease in functioning renal mass. In patients with selective hypoaldosteronism and chronic renal insufficiency, mineralocorticoid administration increases renal acid excretion directly by increasing renal hydrogen ion secretion, and indirectly by correcting hyperkalemia, the latter allowing ammonium production and excretion to increase [23].

Chronic dietary potassium loading. The importance of hyperkalemia in the development of metabolic acidosis due to mineralocorticoid deficiency has been verified. In patients with adrenal insufficiency, correction of hyperkalemia with cation exchange resins significantly increases net acid excretion (ammonium excretion) and corrects the metabolic acidosis, even in the absence of aldosterone administration [40, 41]. Using micropuncture studies in immature rats, we have shown that whole-kidney ammonium excretion falls significantly in vivo in a model of chronic dietary potassium loading [26]. This decrease in excretion was associated with a marked reduction in whole-kidney ammonium production, which occurred despite coexistent chronic metabolic acidosis. Nevertheless, chronic hyperkalemia did not affect net secretion of ammonium by the superficial proximal convoluted tubule. Chronic hyperkalemia impairs accumulation of ammonium in the inner medulla and significantly compromises the transfer of ammonium into the IMCD [27], at least in part by inhibition of active ammonium absorption by the medullary TALH. Therefore, hyperkalemia can lead to metabolic acidosis as a result of a decrease in ammonium excretion. The tendency for metabolic acidosis to develop as a consequence of hyperkalemia might depend on the degree of remaining functional renal mass and the integrity of the renin-aldosterone system [33, 40].

Clinical disorders. The coexistence of hyperkalemia and hyperchloremic metabolic acidosis suggests generalized distal tubule dysfunction. Generalized distal nephron dysfunction manifests as a hyperchloremic hyperkalemic metabolic acidosis, in which urinary ammonium excretion is invariably depressed and renal glomerular function is often compromised. Although hyperchloremic metabolic acidosis and hyperkalemia occur with regularity in advanced renal insufficiency, patients identified and studied simply because of severe hyperkalemia (>5.5 mEq/liter), for example, those with diabetic nephropathy and/or tubulointerstitial disease, have hyperkalemia that is disproportionate to the reduction in glomerular filtration rate. The transtubular potassium gradient [2] is usually low in patients with this disorder (<8), indicating that the collecting tubule is not responding appropriately to the prevailing hyperkalemia. In such patients, a unique dysfunction of potassium and acid secretion by the collecting tubule is attributed to either hypoaldosteronism [42, 43] or to a decrease in effectiveness of aldosterone [44]. Thus, in patients presenting with this constellation of findings, an evaluation of renin-aldosterone elaboration is indicated. A classification of the clinical disorders associated with hyperkalemia and acidification defects is proposed in Table 3.

Table 3. Pathophysiologic classification of disorders associated with hyperkalemic hyperchloremic metabolic acidosis

Mineralocorticoid deficiency
Primary
Generalized (Addison's disease)
Isolated (selective aldosterone deficiency)
Secondary
Hyporeninemic
Pharmacologic
Mineralocorticoid resistance
Pseudohypoaldosteronism type 1
Renal tubular dysfunction
Voltage defects
Secondary to drugs that interfere with Na^+ channel function
Pseudohypoaldosteronism type 2
Secondary to tubulointerstitial disease (pseudohypoaldosteronism type 3)
Hydrogen ion pump defect
Aldosterone deficiency
Obstructive uropathy

Mineralocorticoid deficiency. Destruction of the adrenal cortex by hemorrhage, infection, invasion by tumors, or autoimmune processes results in Addison's disease, that is, combined glucocorticoid and mineralocorticoid deficiency. Causes of Addison's disease include tuberculosis, autoimmune adrenal failure, 21-hydroxylase deficiency, fungal infections, adrenal hemorrhage, metastasis, lymphoma, AIDS, amyloidosis, and drug toxicity (ketoconazole, fluconazole, phenytoin, rifampin, and barbiturates) [44, 45]. Addison's disease is manifest by hypoglycemia, anorexia, weakness, hyperpigmentation, and a failure to respond to stress. These defects can occur in association with renal salt wasting and hyponatremia, low plasma aldosterone levels, high levels of plasma renin activity (PRA), and hyperkalemia and metabolic acidosis [42–45]. The metabolic acidosis of mineralocorticoid deficiency results from a decrease in hydrogen ion secretion in the collecting duct secondary to decreased H^+-ATPase number and function. The hyperkalemia of mineralocorticoid deficiency, in turn, decreases ammonium production and excretion.

In contrast to the less common primary adrenal disorder, patients with hyporeninemic hypoaldosteronism exhibit low plasma renin activity. Patients are usually older (mean age, 65 years) and commonly exhibit mild to moderate renal insufficiency (70%) and acidosis (50%) in association with chronic hyperkalemia (5.5–6.5 mEq/liter) [43, 46]. The most frequently associated renal diseases are diabetic nephropathy and tubulointerstitial disease, systemic lupus erythematosus, and AIDS nephropathy [44]. For 80% to 85% of such patients, there is a reduction in plasma renin activity that cannot be stimulated by the usual physiologic maneuvers. Aldosterone secretion, while low, can be increased by administration of angiotensin II or ACTH. Since approximately 30% of patients with hyporeninemic hypoaldosteronism are hypertensive, the finding of a low plasma renin in these patients suggests a volume-dependent form of hypertension with physiologic suppression of renin production [46]. In general, patients with more advanced renal insufficiency as a result of glomerular disease rather than tubulointerstitial disease (for example, diabetic nephropathy) are more commonly volume expanded [44, 47]. Because either mild salt wasting or salt retention can occur in this disorder, the precise cause of the decrease in plasma renin has not been established firmly. As I mentioned, impaired ammonium excretion is the combined result of hyperkalemia, impaired ammoniagenesis, a reduction in nephron mass, reduced proton secretion, and impaired transport of ammonium by nephron segments in the inner medulla [31, 44].

Isolated hypoaldosteronism, which can occur in critically ill patients, particularly in the setting of severe sepsis or cardiogenic shock, is manifest by markedly elevated ACTH and cortisol levels in association with a decrease in aldosterone elaboration in response to angiotensin II [48]. This hypoaldosteronism might be secondary to selective inhibition of aldosterone synthase as a result of hypoxia, release of cytokines such as TNFα or IL-1, or, alternatively, high circulating levels of atrial natriuretic peptide (ANP) [49]. The features of hypoaldosteronism, including hyperkalemia and metabolic acidosis, can be potentiated by the administration of potassium-sparing diuretics, potassium loads in parenteral nutrition solutions, or heparin, which suppresses aldosterone synthesis in the critically ill patient [50].

Mineralocorticoid resistance. Pseudohypoaldosteronism (PHA) is characterized by renal resistance to the action of aldosterone. The clinical features include hyperkalemia (which can be attributed to impaired potassium secretion), normal or elevated aldosterone levels, and hyperkalemic hyperchloremic metabolic acidosis. By definition, physiologic mineralocorticoid replacement therapy does not correct the hyperkalemia. Mineralocorticoid resistance with hyperkalemia can be associated with salt retention or with salt wasting. Pseudohypoaldosteronism type 1, first described in infants with severe salt wasting, hypotension, and hyperkalemia, is inherited as either an autosomal recessive or dominant disorder. The collecting tubule is unresponsive to aldosterone, and some patients demonstrate resistance in other target organs [51]. This disorder appears to be the result of a loss-of-function mutation in the α or β subunit of the epithelial sodium channel (ENaC) [52]. Adult patients have been reported with hyperkalemia, hyperchloremic metabolic acidosis, hypertension, normal renal function, undetectable plasma renin activity, and low aldosterone levels (pseudohypoaldosteronism type II) [44]. These patients generally have not exhibited glomerular or tubulointerstitial disease. The acidosis is mild and can be accounted for solely by the magnitude of hyperkalemia. Furthermore, renal potassium secretion is resistant to mineralocorticoid administration. Renin and aldosterone levels increase if volume expansion is corrected by diuretics or salt restriction. In careful studies, Schambelan et al demonstrated that potassium excretion responds to sodium sulfate infusion but not to sodium chloride infusion [53]. They then suggested that this disorder results from an early distal tubule "chloride shunt." The "shunt" is viewed as the result of increased chloride reabsorption in the early distal tubule, which would, by decreasing transepithelial voltage, reduce the driving force for potassium secretion. Thiazide diuretics consistently correct the hyperkalemia and metabolic acidosis, as well as the hypertension and plasma aldosterone and plasma renin levels; thus it would be reasonable to assume that this disorder stems from increased activity of the thiazide-sensitive Na^+-Cl^- cotransporter in the connecting tubule [44]. Nevertheless, genetic linkage studies have failed to establish such a relationship [54]. Pseudohypoaldosteronism can be distinguished from selective hypoaldosteronism by the presence of hypertension and normal renal function, the absence of diabetes mellitus and salt wasting, and the failure to exhibit a kaliuretic response to mineralocorticoids. Some authors have described a third type of PHA, which

Table 4. Acquired renal tubular secretory defects associated with hyperkalemic hyperchloremic metabolic acidosis[a]

Sickle-cell disease
SLE
Renal transplant rejection
Obstructive uropathy
Medullary cystic disease
Drug-induced interstitial nephritis
Analgesic abuse nephropathy
HIV nephropathy
IgM monoclonal gammopathy

[a] Usually associated with decreased renin secretion and impaired response of collecting tubule to aldosterone.

Table 5. Drug-induced hyperkalemia

Impaired renin-aldosterone elaboration
Cyclo-oxygenase inhibitors
β-adrenergic antagonists
Converting-enzyme inhibitors
Heparin
Inhibitors of renal potassium secretion
Potassium-sparing diuretics
Trimethoprim
Pentamidine
Cyclosporine A
Digitalis overdose
Lithium
Altered potassium distribution
Insulin antagonists (somatostatin, diazoxide)
β-adrenergic antagonists
α-adrenergic agonists
Hypertonic solutions
Digitalis
Succinylcholine
Arginine hydrochloride, lysine hydrochloride

occurs in adults with overt salt wasting and tubulointerstitial disease but without hypertension [55].

Table 4 outlines a number of renal diseases that are commonly associated with deficient renin elaboration and an attenuated responsiveness to aldosterone, hyperkalemia, and on occasion tubulointerstitial involvement [55–57]. Although hyperkalemia is more likely to be associated with metabolic acidosis and reduced ammonium excretion when the GFR is below 20–50 ml/min, in these disorders significant hyperkalemia can occur with significantly less renal functional impairment. Hyperkalemia out of proportion to the degree of renal insufficiency typically occurs with the nephropathies associated with sickle cell disease, systemic lupus erythematosus, and obstruction of the collecting system; with acute and chronic renal allograft rejection; in hypoaldosteronism; and occasionally in patients with multiple myeloma and amyloidosis [53].

An additional disorder that results in hyperkalemic hyperchloremic metabolic acidosis has been dubbed hyperkalemic distal RTA because of the coexistence of hyperkalemia with the patient's inability to acidify the urine ($U_{pH} > 5.5$) during spontaneous acidosis or following an acid load [58]. The hyperkalemia results from impaired renal potassium secretion, and the TTKG or FE_{K^+} is invariably lower than that expected for hyperkalemia [56]. Urinary ammonium excretion is reduced, but aldosterone levels can be low, normal, or even increased. This variability in aldosterone levels assists in distinguishing this disorder from selective hypoaldosteronism. Moreover, in selective hypoaldosteronism, the urinary pH is low, and the defect in urinary acidification is attributed to the decrease in ammonium excretion and hydrogen secretion. Hyperkalemic distal RTA, which is assumed to be the result of a "voltage defect" in the cortical collecting duct, appears to occur in a variety of renal diseases [56, 57]. Nevertheless, in patients with hyperkalemic RTA and hypoaldosteronism, no evidence for such a defect could be demonstrated [58]. It was concluded that acidification was impaired as a result of abnormal function of the hydrogen ion secretory pump (H^+-ATPase).

Drugs can impair renin or aldosterone elaboration or cause mineralocorticoid resistance, which mimics the clinical manifestations of the acidification defect that occurs with the generalized form of distal RTA with hyperkalemia (Table 5). Cyclo-oxygenase inhibitors (nonsteroidal anti-inflammatory drugs) can generate hyperkalemia and metabolic acidosis as a result of inhibition of renin release [53]. Beta-adrenergic antagonists cause hyperkalemia because they alter potassium distribution and interfere with the renin-aldosterone system. Heparin impairs aldosterone synthesis as a result of direct toxicity to the zona glomerulosa, leading to inhibition of aldosterone synthase. Angiotensin-converting-enzyme (ACE) inhibitors interrupt the renin-angiotensin system and cause hypoaldosteronism with hyperkalemia and acidosis, particularly in patients with advanced renal insufficiency and those with a tendency to develop hyporeninemic hypoaldosteronism, such as those with diabetic nephropathy [56]. The combination of potassium-sparing diuretics and ACE inhibitors should be avoided assiduously.

Spironolactone, a competitive inhibitor of aldosterone, frequently causes hyperkalemia and metabolic acidosis when administered to patients with renal insufficiency [44, 56]. Similarly, amiloride and triamterene can have the same effect [53, 59]. Both potassium-sparing diuretics block the apical Na^+-selective channel in the collecting duct principal cell and thus alter the driving force for potassium secretion. Amiloride is the prototype for a growing number of agents that cause hyperkalemia, including trimethoprim and pentamidine, particularly in patients with AIDS. Trimethoprim and pentamidine are related structurally to amiloride and triamterene; all these agents are heterocyclic, weak bases that exist primarily in the protonated forms in an acidic urine [60]. Kleyman and Ling demonstrated that the protonated forms of both trimethoprim and pentamidine inhibit the epithelial sodium-selective channel in A6 distal nephron cells [60, 61]. This effect in A6 cells has been verified in rat late distal tubules perfused in vivo [62]. Hyperkalemia has been observed in 20% to 53% of HIV-infected patients receiving high-dose trimethoprim (TMP)-sulfamethoxazole (SMX) or TMP-dapsone for the treatment of opportunistic infections, and in as many as 100% of patients with AIDS-associated infections (*Pneumocystis carinii*) receiving pentamidine for more than 6 days [62]. Because both TMP and pentamidine decrease the electrochemical driving force for both potassium and hydrogen secretion in the CCT (Fig. 3), metabolic acidosis frequently accompanies the hyperkalemia, even in the absence of severe renal failure, adrenal insufficiency, severe tubulointerstitial disease, or hypoaldosteronism. While it has been assumed widely that such a "voltage" defect could explain the decrease in hydrogen ion secretion, it is likely that hyperkalemia plays a significant role in the development of the metabolic acidosis through a decrease in ammonium production

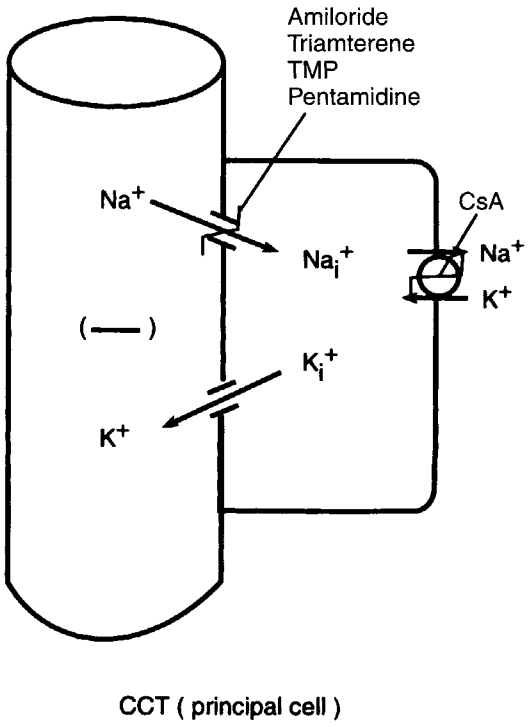

Fig. 3. *Mechanisms of drug-induced voltage defects in the cortical collecting tubule that inhibit K^+ secretion.* Apical Na^+ channel blocked by amiloride, triamterene, trimethoprim (TMP), and pentamidine, and basolateral Na^+, K^+-ATPase by cyclosporine A (CsA).

and excretion. Ammonium excretion has not been systematically investigated in patients with hyperkalemia receiving either TMP or pentamidine thus far, however.

Cyclosporine A (CsA) is associated with hyperkalemia in the transplant recipient. This drug inhibits basolateral Na^+,K^+-ATPase, thereby decreasing intracellular [K^+] and the transepithelial potential, which together decrease the driving force for potassium secretion [63]. Sands et al have suggested that the specific mechanism of CsA inhibition of the sodium pump is through inhibition by this agent of calcineurin activity [64]. Cyclosporine also could decrease the filtered load of potassium through hemodynamic mechanisms, such as vasoconstriction, which decrease GFR and alter the filtration fraction. Additional mechanisms by which CsA might cause hyperkalemia and metabolic acidosis include mineralocorticoid resistance [65], a distal hydrogen pump defect [66], and impairment of the apical membrane potassium-selective channel.

Treatment

Documentation of the background upon which hyperkalemic hyperchloremic metabolic acidosis is expressed provides the basis for appropriate therapy. Of particular importance is a careful drug and dietary history. Contributing or precipitating factors include: low urinc flow or decreased distal sodium delivery, a rapid decline in GFR (especially in acute superimposed on chronic renal failure), hyperglycemia or hyperosmolality, and unsuspected sources of exogenous potassium intake. The workup should include evaluation of the TTKG and its response to furosemide and fludrocortisone, an estimate of renal ammonium excretion (urine net charge, urine osmolar gap, and urine pH), and evaluation of PRA and aldosterone secretion. The last can be obtained under stimulated conditions utilizing dietary salt restriction and furosemide-induced volume depletion.

The decision to treat often is based on the severity of the hyperkalemia. A reduction in serum potassium often improves the metabolic acidosis by increasing ammonium excretion as potassium levels return to the normal range [44]. Patients with combined glucocorticoid and mineralocorticoid deficiency should receive both adrenal steroids in replacement dosages. Patients with hyporeninemic hypoaldosteronism usually respond to a cation-exchange resin (sodium polystyrene sulfonate), alkali therapy, or treatment with a loop diuretic. Volume depletion should be avoided unless the patient is volume overexpanded or hypertensive. Supraphysiologic doses of mineralocorticoids are sometimes necessary but should be administered cautiously in combination with a loop diuretic to avoid volume overexpansion or aggravation of hypertension [56]. Infants with pseudohypoaldosteronism type I should receive a salt supplement in amounts sufficient to correct the syndrome and allow normal growth; patients with pseudohypoaldosteronism type II should receive thiazide diuretics along with dietary salt restriction [44]. Although it seems prudent to discontinue drugs identified as likely causes of the hyperkalemia, this is not always feasible in the patient with a life-threatening disorder, for example, during TMP-SMX or pentamidine therapy in the atovaquone (Mepron)-sensitive AIDS patient with *Pneumocystis carinii* pneumonia. The mechanism by which TMP and pentamidine cause hyperkalemia (voltage defect) might lead one to reason that the delivery to the cortical collecting duct of a poorly reabsorbed anion might improve the electrochemical driving force, favoring potassium and hydrogen secretion. The combined use of acetazolamide with sufficient sodium bicarbonate to deliver significant amounts of bicarbonate to the cortical collecting tubule, thereby increasing the negative transepithelial voltage, theoretically could increase potassium and hydrogen ion secretion [63]. Obviously, with such an approach, aggravation of metabolic acidosis by excessive acetazolamide or insufficient sodium bicarbonate administration must be avoided. This approach, however, has not yet been corroborated by clinical trials.

In summary, hyperkalemia plays a pivotal role in the kidney's response to metabolic acidosis. Hyperkalemia impairs ammonium production and transport in the proximal tubule, as well as ammonium transport in the thick ascending limb of Henle's loop and the medullary collecting duct. The competitive inhibition by hyperkalemia of thick limb absorption in turn impairs the countercurrent system in the renal medulla, which reduces ammonium entry into the inner medullary collecting duct, thus decreasing net acid excretion. This cascade of events is most commonly seen in hyperkalemic hyperchloremic metabolic acidosis as a result of impaired renin release or angiotensin formation, aldosterone secretion or action, or collecting tubule sodium transport. These disorders, often associated with a generalized defect in potassium and hydrogen ion secretion in the collecting duct, are sometimes designated collectively as type-IV distal renal tubular acidosis. Several drugs related structurally to amiloride, such as trimethoprim and pentamidine, impair sodium absorption by interfering with the epithelial sodium channel in the apical membrane of the collecting duct. As a result of impaired sodium absorption, a "voltage" lesion occurs that compromises potassium secretion

secondarily. Clinical assessment of potassium secretion is provided by calculation of the fractional excretion of potassium or the transtubular potassium gradient. In addition, the ammonium concentration in the urine can be estimated in the acidotic patient by calculation of the urine net charge. Treatment should be directed toward correction of the hyperkalemia, restoration of euvolemia, adequate alkali therapy, loop diuretics, and dietary potassium restriction. In severe hypoaldosteronism, the effect of loop diuretics can be augmented significantly by administration of small doses of mineralocorticoid. Fludrocortisone should be used cautiously, however, and avoided in the presence of hypertension or congestive heart failure.

Questions and answers

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): As you know, Ang II itself has now been regarded as an important modulator of proximal acidification processes as well as of renal ammonia production and transport [67, 68]. Could you please comment on the potential direct effects of Ang II in the acidification defect of hyporeninemic hypoaldosteronism?

DR. DUBOSE: Clearly, more investigation is needed to elucidate the role of angiotensin II in the development of metabolic acidosis in association with hyporeninemia. As you mentioned, it is well established that Ang II increases bicarbonate absorption in the S_1 segment by inhibiting adenylyl cyclase. The principal pathway for selective addition of ammonium into the proximal tubule is through substitution of ammonium on the apical sodium/proton exchanger. Nagami has shown that luminal Ang II increases selective ammonium addition in the proximal tubule in parallel with stimulation of luminal acidification [68]. In hyporeninemic hypoaldosteronism per se, one would anticipate a marked reduction in ammonium secretion in the proximal tubule. In our model of selective aldosterone deficiency, we did not specifically examine proximal ammonium secretion. Angiotensin II inhibitors may be associated with hyperkalemia and metabolic acidosis, of course, but this complication appears to occur when there has been tubulointerstitial disease and/or a significant reduction in renal mass. Our models predict that in this setting, both potassium and hydrogen ion secretion are impaired in the collecting duct. Hyperkalemia further compromises net acid excretion by inhibiting both ammonium production and excretion. The effect of Ang II on ammonium transport in the inner medulla has not been examined directly, however.

DR. MADIAS: In reflecting on the acidification defect of hyporeninemic hypoaldosteronism, one would expect features of a voltage-dependent acidification defect. Yet patients with hyporeninemic hypoaldosteronism don't exhibit sodium wasting unless placed on severe sodium restriction, and they maintain the ability to acidify the urine normally. Do you think that the basic acidification defects underlying hyporeninemic hypoaldosteronism and hyperkalemic distal RTA are essentially the same but quantitatively more expressed in the latter syndrome?

DR. DUBOSE: I agree that these disorders appear to represent a continuum of the same defect. In the model of selective aldosterone deficiency, I believe that the bulk of the evidence is more compatible with a "pump" defect rather than with a "voltage" defect. Support for this point of view is provided by studies in both the turtle bladder and the isolated perfused collecting tubule. It is clear that aldosterone directly and specifically impairs proton pump function in the outer medullary collecting duct, where "voltage" would not be a factor. Aldosterone deficiency therefore appears to compromise the function or reduce the number of proton pumps in the membrane.

DR. JOHN T. HARRINGTON (*Dean ad interim, Tufts University School of Medicine, Boston, Massachusetts*): I have two questions. First, in regard to the TTKG, could you tell us the validity, sensitivity, specificity, etc., supporting the concept that a ratio of less than 8 signifies renal hyperkalemia, or is that figure simply an arbitrary definition? Second, why do only 50% or so of patients with hyporeninemic hypoaldosteronism actually have metabolic acidosis? Shouldn't it be 100%?

DR. DUBOSE: The TTKG represents a simple computation that helps place the pathophysiology of hyperkalemia into perspective. It should be viewed as nothing more than a diagnostic aid, not a definitive test. The validity of the TTKG has not been tested rigorously, but there are numerous assumptions and potential pitfalls.

To answer your second question, I don't know why 100% of patients with isolated hypoaldosteronism don't develop metabolic acidosis. There are a number of mechanisms by which ammonium excretion can be increased to compensate for simple hyperkalemia. The simultaneous occurrence of metabolic acidosis and hyperkalemia seems to require either aldosterone deficiency or resistance, a decrease in functional renal mass, or impaired tubular transport.

DR. MADIAS: Are there good observations on the level of plasma aldosterone in patients with hyporeninemic hypoaldosteronism following correction of the hyperkalemia?

DR. DUBOSE: A few studies have examined this question indirectly. Szylman and colleagues first showed that correction of hyperkalemia by Kayexalate was associated with repair of metabolic acidosis [69]. This repair of acidosis occurred in tandem with an increase in urinary ammonium excretion. These changes took place irrespective and independent of aldosterone; pharmacologic doses of fludrocortisone did not correct the hyperkalemia or the acidification defect.

DR. JAMES STROM (*Division of Nephrology, St. Elizabeth's Hospital, Brighton, Massachusetts*): What distinguishes pseudohypoaldosteronism type II from hyporeninemic hypoaldosteronism? If I understood your categorization correctly, the groups have similar hormone levels and may require similar supraphysiologic replacement of mineralocorticoid.

DR. DUBOSE: Patients with hyporeninemic hypoaldosteronism often have significant renal insufficiency. Pseudohypoaldosteronism type II can occur with a normal GFR. These latter patients are resistant to large doses of mineralocorticoid and are volume-expanded. The primary abnormality in PHA type II has been proposed to be of tubular origin, the "chloride shunt," or increased Cl^- transport, which causes the volume expansion, hypertension, and hyperkalemic metabolic acidosis.

DR. AJAY SINGH (*Division of Nephrology, New England Medical Center*): Among patients with hyporeninemic hypoaldosteronism, there appear to be a significant number in whom aldosterone secretion cannot be independently stimulated by ACTH or angiotensin II [70, 71]. This would suggest that other factors play a role in suppressing aldosterone. Indeed, one study suggests that ANP is this factor [72]. Can you comment on this phenomenon and update us on any recent studies that might have examined this issue?

DR. DUBOSE: The consensus has been that when renin is depressed as a result of volume expansion, aldosterone production will not increase in response to hyperkalemia. Insulin deficiency also might play a role. As you point out, a deficient response of ANP to volume expansion can accompany PHA type II or Gordon's syndrome, but there is no direct information to support such an association.

DR. GEETHA NARAYAN (*Division of Nephrology, St. Elizabeth's Hospital*): It has been postulated that severe volume depletion can help perpetuate even simple metabolic acidosis, such as acidosis resulting from diarrhea. It also has been postulated that this may result from a reversible distal acidification defect, resulting in decreased ammonium excretion. Can you comment on this, and is this defect caused by decreased sodium availability in the distal nephron, coupled with more efficient chloride absorption, producing a voltage-type defect?

DR. DUBOSE: Yes, in the scenario you describe, decreased delivery of sodium ultimately could lead to impaired potassium and hydrogen ion secretion, which would reduce net acid excretion and cause metabolic acidosis. However, it is not necessary to superimpose a chloride shunt, because this lesion causes volume expansion. Extremely low distal sodium delivery or impaired sodium absorption should be sufficient.

DR. NARAYAN: Is the effect of hyperkalemia on ammonium production still believed to be mediated, at least in part, through transcellular cation exchange and intracellular alkalosis?

DR. DUBOSE: Hyperkalemia decreases the uptake of glutamine and decreases production of ammonium from glutamine precursors. Although the cellular mechanism has not been defined precisely, it is known that uptake is enhanced by intracellular acidosis. Whether intracellular alkalosis develops in the proximal tubule cell during hyperkalemia, or whether it plays a role in the decrease in ammonium excretion, is not known. In a model of hyperkalemic metabolic acidosis, David Good and I attributed the decrease in ammonium excretion to changes in transport beyond the proximal tubule [26]. This defect was later localized to the renal medulla [27]. While ammonium production was reduced by 50% and excretion by 40%, there was no change in net ammonium transport in the proximal tubule. Such a disassociation of proximal production and transport conceivably could occur in response to intracellular alkalosis. Nevertheless, this effect could be modulated by the peritubular potassium concentration, which clearly alters proximal ammonium secretion.

DR. MADIAS: As you know, some work suggests that ammonia can exert injurious effects on the kidney by augmenting interstitial fibrosis via complement activation [73]. In this context, the decreased ammonia production in tubulointerstitial diseases might be teleologically adaptive. On the other hand, metabolic acidosis has its own adversity [74]. Can you reflect a bit on this issue?

DR. DUBOSE: The interesting study you mentioned [73] suggested that ammonia in the inner medulla could activate the alternate complement pathway, which could lead to tissue injury in the form of tubulointerstitial disease. One might speculate that in tubulointerstitial disease a decrease in ammonium absorption in the thick limb and a decrease in ammonia accumulation in the inner medulla might be beneficial in slowing perpetuation of the injury, as you suggest. This model has not been developed further, however, and additional work is needed in this area.

DR. HARRINGTON: I have two questions regarding the concept of direct ammonium secretion. First, how do you specifically measure direct ammonium secretion across the distal nephron? Second, of the total amount of ammonium excreted, how much is via direct ammonium secretion versus ammonia combining with hydrogen to be excreted as ammonium?

DR. DUBOSE: The precise delineation of which moiety is secreted requires consideration of the pK′ of ammonium, the pH of tubule fluid, the total ammonia concentration, and transepithelial potential. To answer your question, each nephron segment's contribution would have to be defined in each physiologic condition. This type of study has not been performed. Since the ammonium excreted is ultimately derived from the ammonium secreted by the proximal tubule, I would speculate that the contribution from the "direct" route exceeds the trapping route by at least twofold.

DR. HARRINGTON: Drawing from your own experience or the literature, can you quantitate the common causes of hyperkalemia in hospital patients? That is, how much of the hyperkalemia is due to disease, and how much is due to administered potassium?

DR. DUBOSE: We have not quantitated such data from our hospital. The sources of exogenous potassium are significant, but I think that the incidence of drug nephrotoxicity as a cause of hyperkalemia is increasing. Patients often receive potassium loads and drugs that are inappropriate for the degree of renal function. Examples include nonsteroidal anti-inflammatory drugs, ACE inhibitors, and potassium-sparing diuretics. At least three groups of patients are at particular risk: (*1*) Patients with HIV or AIDS, with a life-threatening infection, who are receiving pentamidine or trimethoprim. (*2*) Patients with diabetes mellitus; very often these patients receive a multitude of drugs including nonsteroidal agents and potassium-sparing diuretics, as well as ACE inhibitors, all of which, especially in combination, can cause severe hyperkalemia and metabolic acidosis. (*3*) Hypoxic patients in the critical care setting who develop selective hypoaldosteronism with or without heparin administration.

DR. SINGH: As you stated, one of the drugs implicated as a cause of drug-induced hypoaldosteronism and hyperkalemia is heparin, which appears to inhibit 18-hydroxylase in the adrenal gland, thereby impeding aldosterone biosynthesis [75, 76]. Given that heparin is used so frequently, I'm surprised that we do not see more hyperkalemia among our patients in the hospital. Is it a dose-related effect? Are other factors important?

DR. DUBOSE: Heparin-associated hyperkalemia is limited to critically ill patients and is not dose-related. As I said, the most common co-morbidity is hypoxemia.

DR. MADIAS: My experience is that even low-dose heparin can produce hyperkalemia but not in the presence of normal renal function. Almost all the patients I have seen have had underlying renal dysfunction or another independent reason for hyperkalemia.

DR. SINGH: Is the development of heparin-induced hyperkalemia observed in patients treated with low-molecular-weight heparin?

DR. DUBOSE: I am not aware of any reports to this effect.

DR. IOANNIS GIATRAS (*Renal Fellow, New England Medical Center*): Does heparin administered during hemodialysis decrease the level of plasma aldosterone?

DR. DUBOSE: I am unaware of any measurements in the literature.

DR. MADIAS: Have you had the opportunity to study the effects of lithium?

DR. DUBOSE: We have studied lithium nephrotoxicity in the rat,

but the lithium model was not associated with hyperkalemia. These animals developed metabolic acidosis as a result of a "pump" defect.

DR. HARRINGTON: You discussed hypokalemia and the impact on ammonium secretion in experimental animals that also had chloride-depletion metabolic alkalosis. What is the effect of diet-induced hypokalemia on ammonium secretion quantitatively in the absence of chloride-depletion metabolic alkalosis?

DR. DUBOSE: We have not studied pure hypokalemia, and I am not aware of any study in humans or in animal models on ammonium transport in hypokalemia without alkalosis.

DR. ANDREW J. KING (*Division of Nephrology, New England Medical Center*): In the treatment of type-IV renal tubular acidosis, is there a role for poorly absorbed anions? If you were going to design an approach that employed poorly absorbed anions, what would you use?

DR. DUBOSE: What you've proposed seems logical. Since sulfate is not tolerated well, bicarbonate is reasonable therapy for a "voltage" lesion. One might need to combine bicarbonate administration with acetazolamide. Furosemide, rather than acetazolamide, might work, as it has other beneficial effects, including an increase in potassium excretion.

DR. MITCHELL S. JACOBSON (*Renal Fellow, Division of Nephrology, New England Medical Center*): Trimethoprim has been described as an important cause of hyperkalemia in patients with AIDS. The dose of trimethoprim in HIV-infected patients is often much greater than that given for conventional infections. However, in rare cases hyperkalemia has been described in elderly patients given conventional doses. In fact, I can recall during my fellowship a diabetic patient taking oral trimethoprim-sulfamethoxazole who developed life-threatening hyperkalemia. Can you comment on the occurrence of hyperkalemia with conventional doses of trimethoprim? What conditions would predispose a patient to hyperkalemia in this setting?

DR. DUBOSE: The same phenomenon has been reported in children taking higher doses of trimethoprim in the absence of significant renal insufficiency. These agents work from the luminal side, so I assume that it is the drug concentration in the urine that matters. It's more likely that hyperkalemia would be observed in prerenal conditions.

DR. HARRINGTON: Could you define disequilibrium pH for the acid-base neophyte?

DR. DUBOSE: Disequilibrium pH is the difference between pH measured in situ and pH attained when the tubule fluid is removed and allowed to come to equilibrium. Obviously this technique applies only to the micropuncture or microperfusion setting.

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